

**CLAIMS:**

- 5        1.        An adeno-associated viral vector comprising a first polynucleotide comprising a first  
         nucleic acid segment that encodes an AAV capsid protein that comprises an  
         exogenous amino acid sequence that binds to a mammalian lipoprotein receptor.
- 10       2.        The vector of claim 1, wherein said capsid protein is a Vp1 or a Vp2 capsid protein.
3.        The vector of claim 1, wherein said exogenous amino acid sequence binds to a  
         mammalian low-density lipoprotein (LDL) or very low density lipoprotein (VLDL)  
15       receptor.
4.        The vector of claim 1, wherein said exogenous amino acid sequence comprises the  
         sequence of any one of SEQ ID NO:1 to SEQ ID NO:21.
- 20       5.        The vector of claim 4, wherein said exogenous amino acid sequence comprises the  
         sequence of SEQ ID NO:19.
- 25

6. The vector of claim 1, wherein said exogenous amino acid sequence comprises the sequence of any one of SEQ ID NO:1 to SEQ ID NO:20, and further comprises the sequence of SEQ ID NO:21.

5

7. The vector of claim 1, wherein said exogenous amino acid sequence comprises the sequence of any one of SEQ ID NO:22 to SEQ ID NO:31.

- 10 8. A recombinant adeno-associated viral expression system comprising:

(a) a first polynucleotide comprising a first nucleic acid segment that encodes an AAV capsid protein that comprises an exogenous amino acid sequence that binds to a mammalian lipoprotein receptor; and

15

(b) a second polynucleotide comprising a second nucleic acid segment that encodes an expressed therapeutic agent.

- 20 9. The recombinant adeno-associated viral expression system of claim 8, wherein said expressed therapeutic agent is a peptide, polypeptide, ribozyme, or antisense molecule.

10. The recombinant adeno-associated viral expression system of claim 8, wherein said exogenous amino acid sequence binds to a mammalian VLDL or LDL receptor.

5 11. The recombinant adeno-associated viral expression system of claim 8, wherein said exogenous amino acid sequence comprises the sequence of any one of SEQ ID NO:1 to SEQ ID NO:20.

10 12. The recombinant adeno-associated viral expression system of claim 11, wherein said exogenous amino acid sequence further comprises the sequence of SEQ ID NO:21.

15 13. The recombinant adeno-associated viral expression system of claim 8, wherein said exogenous amino acid sequence comprises the sequence of any one of SEQ ID NO:22 to SEQ ID NO:31.

20 14. The recombinant adeno-associated viral expression system of claim 8, wherein said first and said second polynucleotides are comprised within a single rAAV vector:

25 15. The recombinant adeno-associated viral expression system of claim 8, wherein said first and said second polynucleotides are comprised on distinct rAAV vectors:

16. The recombinant adeno-associated viral expression system of claim 8, wherein said second polynucleotide further comprises a promoter operably linked to said second nucleic acid segment, wherein said promoter expresses said therapeutic agent.

5

17. The recombinant adeno-associated viral expression system of claim 16, wherein said promoter is a heterologous, tissue-specific, constitutive or inducible promoter.

10

18. The recombinant adeno-associated viral expression system of claim 17, wherein said promoter is selected from the group consisting of a CMV promoter, a  $\beta$ -actin promoter, an insulin promoter, a hybrid CMV promoter, a hybrid  $\beta$ -actin promoter, an EF1 promoter, a U1a promoter, a U1b promoter, a Tet-inducible promoter and a VP16-LexA promoter.

15

19. The recombinant adeno-associated viral expression system of claim 18, wherein said promoter is a mammalian  $\beta$ -actin promoter.

20

20. The recombinant adeno-associated viral expression system of claim 8, wherein said second polynucleotide further comprises an enhancer sequence operably linked to said second nucleic acid segment.

25

21. The recombinant adeno-associated viral expression system of claim 20, wherein said enhancer sequence comprises a CMV enhancer, a synthetic enhancer, a liver-specific enhancer, a lung-specific enhancer, a muscle-specific enhancer, a kidney-specific enhancer, a pancreas-specific enhancer, or an islet cell-specific enhancer.

22. The recombinant adeno-associated viral expression system of claim 21, wherein said enhancer sequence comprises a CMV enhancer.

23. The recombinant adeno-associated viral expression system of claim 8, wherein said second nucleic acid segment further comprises a post-transcriptional regulatory sequence.

24. The recombinant adeno-associated viral expression system of claim 23, wherein said regulatory sequence comprises a woodchuck hepatitis virus post-transcription regulatory element.

25. The recombinant adeno-associated viral expression system of claim 8, comprised within a mammalian host cell.

26. The recombinant adeno-associated viral expression system of claim 25, wherein said mammalian host cell is a pancreatic, kidney, muscle epithelial, liver, heart, lung, or brain cell.

5

27. The recombinant adeno-associated viral expression system of claim 26, wherein said mammalian host cell is a human pancreatic islet cell.

10

28. The recombinant adeno-associated viral expression system of claim 9, wherein said polypeptide is selected from the group consisting of  $\alpha_1$ -antitrypsin (AAT), a growth factor, an interleukin, an interferon, an anti-apoptosis factor, and a cytokine.

15

29. The recombinant adeno-associated viral expression system of claim 28, wherein said polypeptide is selected from the group consisting of BDNF, CNTF, CSF, EGF, FGF, G-SCF, GM-CSF, gonadotropin, IFN, IFG-1, M-CSF, NGF, PDGF, PEDF, TGF, TGF-B2, TNF, VEGF, prolactin, somatotropin, XIAP1, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-10(I87A), viral IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, and IL-18.

20

30. A recombinant adeno-associated virus virion comprising the vector of claim 1, or the recombinant adeno-associated viral expression system of claim 8.

25

31. The recombinant adeno-associated virus virion of claim 30, wherein said virion is selected from the group consisting of AAV serotype 1, AAV serotype 2, AAV serotype 3, AAV serotype 4, AAV serotype 5, and AAV serotype 6.

5

32. A plurality of adeno-associated viral particles comprising the vector of claim 1 or the recombinant adeno-associated viral expression system of claim 8.

10

33. A mammalian cell comprising the vector of claim 1, or the recombinant adeno-associated viral expression system of claim 8.

15

34. The mammalian cell of claim 33, wherein said cell is a human endothelial, islet, hepatocyte, pancreas, kidney, muscle, spleen, liver, heart, lung, or brain cell.

20

35. A composition comprising the vector of claim 1, the recombinant adeno-associated viral expression system of claim 8, the recombinant adeno-associated virus virion of claim 32, the plurality of adeno-associated viral particles of claim 33; or the mammalian host cell of claim 34.

36. The composition of claim 35, further comprising a pharmaceutical excipient, buffer, or diluent.

5 37. The composition of claim 36, formulated for administration to a human.

38. The composition of claim 35, further comprising a liposome, a lipid, a lipid complex, a microsphere, a microparticle, a nanosphere, or a nanoparticle.

10

39. The composition of claim 35, for use in therapy.

15 40. The composition of claim 39, for use in cancer, diabetes, autoimmune disease, pancreatic disease, or liver disease therapy.

20 41. Use of a composition according to claim 35, in the manufacture of a medicament for treating cancer, diabetes, autoimmune disease, pancreatic dysfunction, or liver dysfunction.

25 42. Use according to claim 41, in the manufacture of a medicament for treating human pancreatic dysfunction.



43. A kit comprising:

5 (a) the adeno-associated viral vector of claim 1, the recombinant adeno-associated viral expression system of claim 8, the virion of claim 30, the viral particles of claim 32, the cell of claim 33, or the composition of claim 35; and

(b) instructions for using said kit.

10 44. A method for targeting an AAV virion or viral particle to a mammalian cell that comprises a cell-surface lipoprotein receptor, said method comprising the step of: providing to a population of cells an AAV virion or viral particle that comprises the  
15 vector of claim 1, or the recombinant adeno-associated viral expression system of claim 8, in an amount and for a time effective to target said virion or said viral particle to cells of said population that express said cell-surface lipoprotein receptor.

20 45. A method for targeting an expressed therapeutic agent to a mammalian cell that comprises a cell-surface lipoprotein receptor, said method comprising the step of providing to a mammal that comprises a population of said cells an amount of the recombinant adeno-associated viral expression system of claim 8.

25

46. The method of claim 45, wherein said expressed therapeutic agent is a peptide, polypeptide, ribozyme, or antisense molecule.

5 47. A method for preventing, treating or ameliorating the symptoms of a disease, dysfunction, or deficiency in a mammal, said method comprising administering to said mammal the virion of claim 30, or the viral particles of claim 32 in an amount and for a time sufficient to treat or ameliorate the symptoms of said disease, dysfunction, or deficiency in said mammal.

10 48. The method of claim 47, wherein said mammal is a human.

15 49. The method of claim 46, wherein said mammal has, is diagnosed with, or is at risk for developing, diabetes or an autoimmune disorder.

20 50. The method of claim 47, wherein said virion or said plurality of viral particles is administered to said mammal intramuscularly, intravenously, subcutaneously, intrathecally, intraperitoneally, or by direct injection into an organ or a tissue.

25 51. The method of claim 50, wherein said organ or tissue is selected from the group consisting of pancreas, liver, heart, lung, brain, kidney, joint, and muscle.